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Review

A Narrative Review of the Evidence Supporting Nutritional Supplementation for Better Muscle Health in Older Adults

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Abstract

Sarcopenia is characterised by progressive and generalised decline in muscle strength, function, and muscle mass. Now recognised as a muscle disease, it is highly prevalent in older adults, with estimates of up to 30% in some populations. Sarcopenia has a complex multifactorial aetiology, including cellular and molecular changes, chronic disease, lower physical activity as well as nutritional deficiency. Sarcopenia is associated with a range of adverse physical and metabolic outcomes leading to disability, morbidity, impaired quality of life and mortality. Given the demographic shifts in the population, there is an urgent need to improve skeletal muscle health in older adults. Unfortunately, there are no pharmacologic therapies suitable for widespread use currently. In this short review, we discuss the existing literature reporting the benefits of various options for nutritional supplementation in older sarcopenic participants or healthy older adults. Several systematic reviews have been

undertaken on this topic with some key findings. In general, supplementation is more effective in combination with resistance exercise. The research literature supports protein and vitamin D supplementation in individuals who are insufficient. There is also evidence in support of supplementation with creatine, leucine with vitamin D, whey supplements and combinations of creatine, whey and leucine. Probiotics may also be beneficial. Further well conducted and standardised research trials are required.

Keywords
Sarcopenia; supplementation; intervention; older people

1. Introduction

Over the coming years, the number of people over the age of 65 is projected to increase substantially. By 2050, 2 billion people will be over 60 years of age, up from 1 billion in 2020 according to the World Health Organization (WHO) [1]. This increase is occurring at an unprecedented pace and will accelerate in coming decades, particularly in developing countries. The occurrence of musculoskeletal health disorders such as sarcopenia will also increase commensurate with population ageing.

Sarcopenia is characterised by progressive and generalised decline in muscle strength, function and muscle mass with increasing age or secondary to disease [2] (Figure 1). It is associated with a range of adverse physical and metabolic outcomes leading to disability, morbidity, impaired quality of life and mortality [3, 4] and has also been identified as a predictor of fracture risk [5]. In terms of cost, sarcopenia incurred an estimated $18.5 billion in health care costs to the USA in 2000 [6]. In the UK, a report in 2019 calculated that the annual excess cost associated with muscle weakness was estimated to be £2.5 billion [7]. Although commonly associated with the ageing process, the development of sarcopenia is recognized to begin earlier in life encompassing muscle generation in utero and growth during child- and adulthood [8]. Muscle fibre size and function is determined by muscle use during physical activity, nutrient availability, and the action of both hormones and growth factors that affect myogenesis-related genes. Muscle mass, and strength increase during childhood and adolescence then remain relatively constant in early adulthood until the start of decline from the late 40 s. The resulting health of muscle in older age is therefore a function of the 'peak' attained in early life and the extrinsic and intrinsic changes operating through middle years into old age [8, 9].

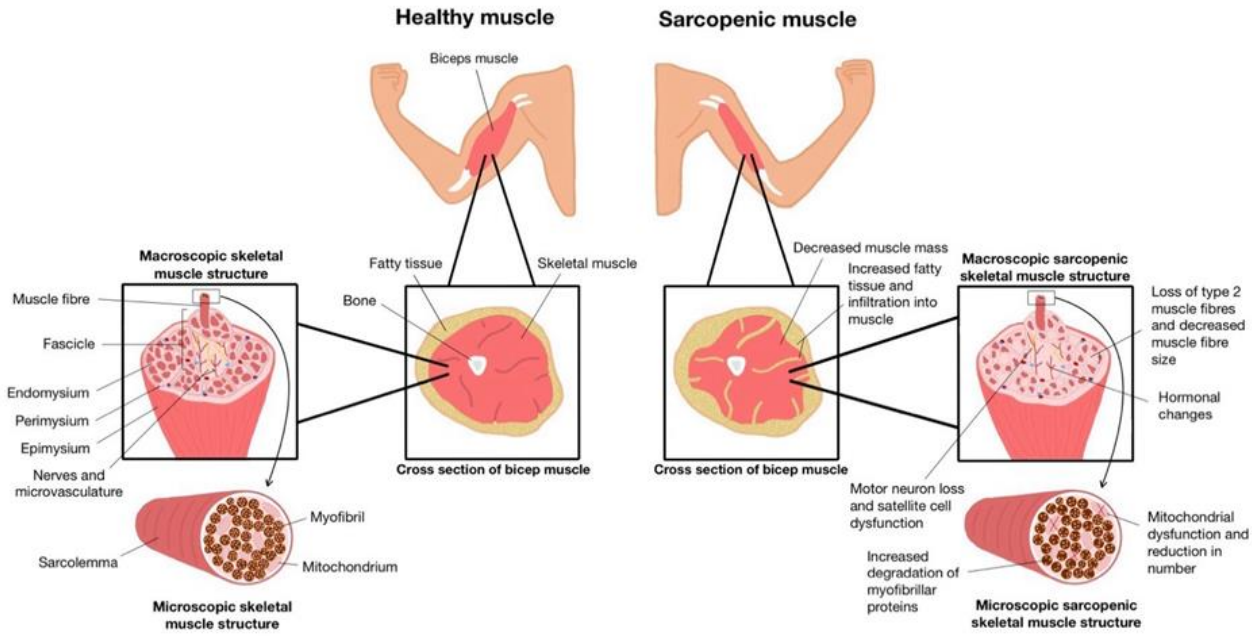

Figure 1 Anatomy of healthy skeletal muscle in comparison to sarcopenic skeletal muscle. Skeletal muscle is composed of many bundles of muscle fibres called fascicles. Fascicles are made up of many individual muscle fibres. Muscle fibres consist of many myofibrils enclosed around a sarcolemma (muscle cell membrane). Myofibrils contain actin and myosin myofilaments. Cellular changes in skeletal muscle in sarcopenia include atrophy of type II myofibers, decrease in fibre size, denervation, decrease in number and function of satellite cells as well as reduction and impaired function of the mitochondrial population. Age related changes in muscle composition and deposition of intermuscular adipose tissue may explain why muscle strength declines more than muscle mass with age.

Several varying definitions of sarcopenia have contributed to differences in prevalence estimates worldwide, ranging from 3-30% [3, 10-12]. Currently, a global definition for sarcopenia does not exist but whilst waiting for consensus from the Global Leadership in Sarcopenia (GLIS) consortium [13], several well-constructed diagnostic algorithms provide a mechanism for clinical case finding [3]. Given the demographic changes that are occurring and the personal and societal costs of sarcopenia, there is an urgent need to prevent and reverse decline in muscle health in older adults. Many nutrients are known to affect muscle health [14-18], and it therefore seems reasonable to consider their role in maintenance skeletal muscle function. The purpose of this review is to describe up to date evidence and identify nutritional or multimodal interventions that can ameliorate the declines in muscle strength and mass, as well as augment muscle protein synthesis in older adults. Searches up to November 2024, were conducted in PubMed and Cochrane databases using medical subject headings and search terms including sarcopenia, muscle protein synthesis, nutritional supplementation, muscle strength, muscle mass. Searches were restricted to human studies reported in English language. Emphasis was placed on randomised controlled trials (RCT), systematic reviews and meta-analyses, scoping reviews or umbrella reviews of meta-analyses. An overview of identified intervention strategies to improve muscle function and performance is shown in Figure 2.

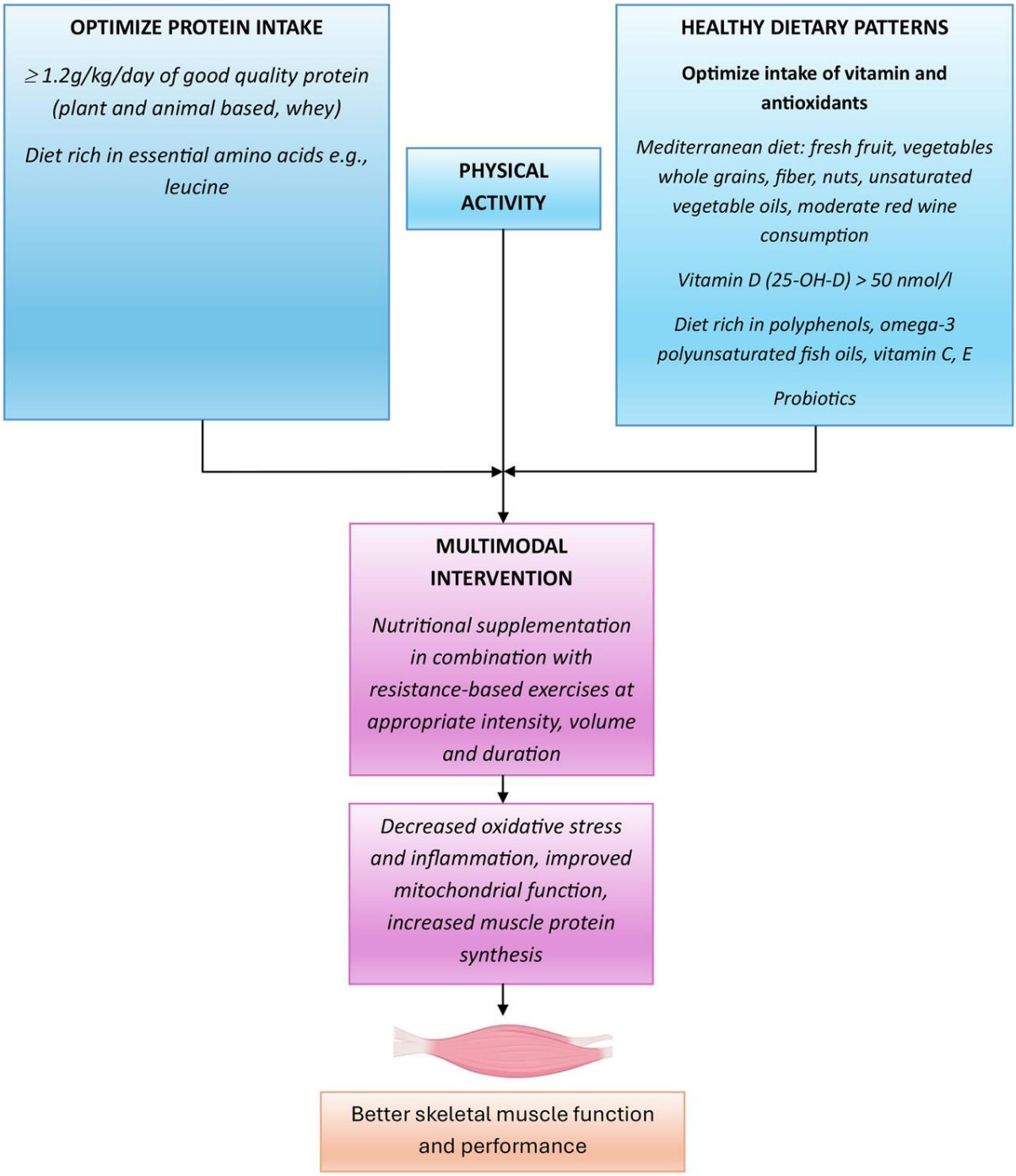

Figure 2 Intervention strategies for sarcopenia. This scheme dictates that adoption of dietary and lifestyle changes including physical activity are beneficial for ameliorating the decline in skeletal muscle strength, function and mass.

2. Non-Pharmacological Management: The Role of Adjunctive Exercise

Before a discussion of nutritional supplementation, it is important to address the contribution of resistance exercise to muscle health. Exercise interventions have been shown to be effective in improving muscle strength and function. For example, in a systematic review and meta-analysis of 23 studies involving 1252 participants, resistance as well as multicomponent exercise interventions

were associated with improved grip strength, knee extension strength, walking speed, general mobility and increase in muscle mass of the lower extremities in older people with sarcopenia [19]. However, safely executing resistance training (RT) can be challenging for older people but clearer guidelines for safely implementing a RT programme in older people have been proposed. For example, Hurst et al. recommend a programme consisting of two sessions a week involving a combination of upper and lower limb resistance exercise with a high degree of effort [20]. Randomised controlled trials (RCTs) have used nutritional supplementation such as protein, creatinine, essential amino acids, β-hydroxy-β-methylbutyrate and vitamin D in combination with exercise and have shown a modest but positive impact on muscle mass and function with greater benefits on physical performance in adults over the age of 60 [21] as well as demonstrating the efficacy of progressive resistance exercise to stimulate muscle protein synthesis [22, 23]. Low repetition, light load power training was also associated with improved knee extensor strength over the course of 6 weeks in a small study of postmenopausal women with sarcopenia [24]. A previous systematic review showed that chronic resistance training is safe and effective in improving muscle mass, strength, and quality but not physical performance [25]. In terms of the type and timing of supplementation, a recent network meta-analysis of 116 trials, comprising 4711 adult participants showed that milk, mixed (protein blends that contain animal and plant-based sources of protein) or animal based protein ingested after exercise appears to be more beneficial in improving muscle strength and mass than placebo alone [26]. Ultimately, there is support for the additive effects of nutritional supplementation to enhance the effects of RT on muscle function in older adults compared with nutritional supplementation exclusively. However, given the heterogeneity of results from RCTs, any intervention will need to be tailored to the intended population to realise the full benefits of this combination [27-30].

2.1 General Nutritional Supplementation

One nutritional approach commonly focuses on Vitamin D, calcium, and protein intake. Despite the lack of information regarding the intake of high-quality protein in older individuals, it has been suggested that adequate intake should be ensured based on the recognition that intake of protein in older people remains low, especially in situations of stress during intercurrent illness. Higher protein intake has been shown to be protective against the decline in physical function in older individuals, including those with a previously sufficient protein intake, independent of physical activity [31] and indeed protein supplementation above the recommended daily amount in combination with resistance exercise or endurance type exercises has been advised by some groups. For example, high quality-protein intake to 1-1.2 g/kg/day by food or supplementation [32, 33]. This combination has demonstrated increase in muscle mass, muscle strength, balance and functional capacity [23, 34].

Perhaps the most considered nutrient for musculoskeletal health is vitamin D. Low level of vitamin D is commonly found in sarcopenic individuals [16-18] and is likely to contribute to muscle weakness and increased risk of falls and hence maintenance of adequate circulating vitamin D level, either through sunlight exposure or dietary intake is important. An adequate vitamin D status is associated with better muscle mass and function [35], and reduced number of falls in postmenopausal women [36], so attention to vitamin D status is important in this context. Vitamin K is also essential for the effective function of proteins but a recent review of the role of vitamin K

in muscle health highlighted methodological differences in research studies making meaningful conclusions difficult to draw [14].

A recent systematic review considered the benefits of exercise in combination with protein supplementation, with additional vitamin supplementation on muscle parameters in older men with sarcopenia [37]. Taken together, researchers highlighted the benefits of resistance exercise with possible additional benefits of aerobic exercise on inflammatory status. They also highlighted potential risks of detraining and also suggested that all protein supplements provided benefit in their analysis of 13 studies. Individual supplements are perhaps more commonly considered and the association of specific supplements with muscle health is outlined below.

2.2 Specific Supplements

2.2.1 Creatine

Creatine, a naturally occurring substance obtained from exogenous sources (red meat, seafood) or endogenous synthesis, is indirectly involved in regeneration of adenosine triphosphate (ATP) and sustains muscular contraction during bursts of activity. Creatine has been extensively researched as a possible therapy for sarcopenia [38]. It can influence ATP resynthesis, as well as calcium flux, inflammation and oxidative stress, among other potential mechanisms. Creatine supplementation has been shown to increase muscle cross-sectional area and strength, particularly when combined with resistance exercise [38-40]. Several systematic reviews and meta-analyses have been undertaken to summarise the available literature, all of which have been broadly positive. These have typically been undertaken as two assessments - the value of creatine in combination with resistance training, or as a supplement alone. Firstly, creatine supplementation in combination with resistance exercise training has been shown to be beneficial for muscle mass and functional performance in older adults [39, 41, 42]. A recent meta-analysis performed in 2021 by Forbes and colleagues [43] suggested that any dose of creatine in combination with resistance exercise training increased lean mass, chest-press and leg-press strength compared with resistance training alone. Further sub-analyses suggested that a creatine loading phase (>20 g/day for first 5-7 days) produced superior improvements and that taking creatine on exercise days was beneficial compared with taking placebo on exercise days. The impact of creatine in combination with whey protein and resistance exercise has also been researched. In general, there has been limited evidence for additional benefit of combined supplementation, but the complexities of different loading patterns and dosages, study populations and outcome measures make it hard to give definitive guidance [38].

2.2.2 Leucine and Its Derivatives

Leucine is an essential amino acid and has been studied extensively in for its effects on skeletal muscle mass and strength. Earlier studies of leucine supplementation did not show benefit. For example, a systematic review and meta-analysis of 16 studies comprising 999 participants [44] explored the effect of leucine supplementation compared to control groups who did not receive leucine. Although leucine increased lean body mass in older persons risk of sarcopenia, it did not increase muscle strength. A recent systematic review considered the benefits of leucine supplementation to muscle health in older adults who are already suffering the effects of muscle ageing [45]. It considered intervention studies in adults >60 years with a history of sarcopenia and

identified 3 studies where leucine supplementation was considered alone; one in combination with exercise; 7 studies that considered leucine and another supplement and 12 that considered leucine, another supplement in combination with exercise. Overall, the systematic review highlighted the combination of leucine with supplements (especially leucine-enriched protein supplements) with or without exercise as the most promising combination. However, as is commonly the case, the heterogeneity of study design makes it hard to provide definitive guidance. Another systematic review identified a total of 17 RCTs enrolling 1418 subjects [46]. Leucine-isolated supplementation showed no effect on total lean mass, grip strength or leg press but leucine-combined supplementation including vitamin D showed a significant improvement in grip strength. Participants included in these studies were older adults with or without a diagnosis of sarcopenia, which may impact public health messaging and clinical recommendations. The synergistic effect with vitamin D was also seen in another meta-analysis of 17 RCTs comprising 1418 older participants with sarcopenia related measures by Guo et al. [47]. Although leucine-isolated supplementation did not improve muscle mass and strength in older people, leucine administration combined with vitamin D was associated with better hand grip strength and gait speed in older adults. In terms of providing an overview of the benefits of leucine supplementation, as well as a combination approach of protein supplementation and exercise, an umbrella review of 15 systematic reviews and meta-analyses suggested leucine consumption was associated with better overall muscle mass in older people with sarcopenia and that the effects of resistance training on both muscle mass and strength are augmented by protein supplementation [48].

As a derivate of leucine, β-hydroxy-β-methylbutyrate (HMB) has been suggested to increase or mitigate the loss of skeletal muscle and improve muscle function. Phillips and colleagues conducted an umbrella review of systematic reviews of HMB supplementation that considered muscle outcomes [49]. They identified 15 systematic reviews that met their inclusion criteria, demonstrating the wealth of literature in this area. Five of 15 studies found some evidence that HMB increased lean soft tissue mass (measured using DXA); the remaining 10 studies reported some evidence favouring no difference (6/10 studies) or insufficient evidence to determine an effect (4/10 studies). Of the 12 studies that considered muscle strength, the findings were very mixed. No study reported a positive effect of HMB on physical function. In addition, the majority of studies could not provide sufficient evidence to generate a recommendation. Taken together, this review suggests that while benefits of supplementation to muscle may be present, these are modest in the absence of resistance exercise.

2.2.3 Whey Protein

Kuo and colleagues investigated the benefits of whey protein on muscle health with or without resistance exercise in women aged 55 years and above [50]. They identified 14 studies that they included in a systematic review and 10 studies that they included in a meta-analysis. Once again, the importance of resistance exercise was highlighted. In the group that also included exercise, whey protein supplementation was associated with significant improvements in lower limb lean-mass. The benefits of combining whey protein supplementation and resistance training were confirmed in a recent systematic review and meta-analysis of 30 studies, comprising 2105 participants aged 60 and over where the combination improved lower body strength but no effect on hand grip strength or physical performance [51].

Potential mechanism of action for whey and soy protein supplementation was considered in a systematic review and meta-analysis undertaken by Prokopidis and colleagues [52]. They identified 31 RCTs that met their inclusion criteria, reporting a significant reduction in circulating IL-6 levels following whey protein supplementation as well as lower TNF-α levels following soy protein supplementation. The addition of soy isoflavones was associated with a further decline in circulating TNF-α levels.

2.2.4 Combination Supplementation

In addition to the studies reported above, a separate oral nutritional supplementation regime consisting of a whey-protein-based, leucine- and vitamin D-enriched formula was considered by Cereda and colleagues [53]. In their systematic review, they identified 10 articles providing efficacy data from eight trials suggesting benefits with or without accompanying resistance exercise in different clinical settings suggesting that this combination may provide an optimal recipe for treating sarcopenia. This was confirmed in a recent scoping review of 11 studies experimenting with whey protein and leucine enriched multi-nutrient formulas high in vitamin D3 with or without combining exercise rehabilitation on measures of sarcopenia in older adults aged 66-86 years. Nutritional interventions appeared to improve body composition, lean mass and physical function with or without exercise in older adults recovering from sarcopenia [54].

2.2.5 Probiotics

It has been suggested that the composition of gut microbiota may impact on skeletal muscle, and may play a part in the development of sarcopenia [55]. Signals generated through interactions within the gut microbiome (microbial metabolites, gut peptides, lipopolysaccharides, and interleukins) regulate muscle functionality through modulation of systemic/tissue inflammation and insulin sensitivity. A recent systematic review and meta-analysis explored the impact of probiotic supplementation on muscle mass, total lean mass and muscle strength [55]. The authors included 24 randomised controlled trials. The study's main analysis reported that muscle mass was improved following probiotics compared with placebo, though no benefits were identified regarding total lean mass. A significant increase in global muscle strength was also observed among six randomised controlled trials. Overall, it appears that there may be some benefits on skeletal muscle health through probiotic supplementation, but further work is required in this area.

2.2.6 Real World Examples

Much of the literature available considers the benefits of protein supplementation and resistance exercise in a 'healthier' older population. In a study by S.de Azevedo Bach and colleagues [56], researchers randomised 31 older adults aged 60-80 years to either whey-protein (20g with breakfast and dinner) or to placebo/maltodextrin. Both groups underwent supervised progressive resistance training twice a week. In this relatively small study, there was no apparent benefit from supplementation as well as exercise, with both groups showing improvements in many outcomes, including muscle mass and the timed up-and-go test.

2.3 Dietary Patterns

Due to the complex relationships that individual dietary components have on skeletal muscle health, recent focus has been on varied dietary patterns consisting of fruits, legumes, whole grains, nuts, fish, lean meat and unsaturated vegetable oils, which are associated with lower all-cause mortality on older people [57]. There is inconsistent evidence on the role of 'healthier diets' on muscle health in general [58]. However, a widely evaluated dietary pattern is the mediterranean diet which comprises higher daily intake of vegetables, fruits, cereals, olive oil, fish as well as red wine consumption in moderate amounts with comparatively lower intakes of red meat, processed meat, sweets and dairy compared to other diets [59]. Whilst the benefits of the Mediterranean diet have been extensively documented in relation to cardiovascular disease, cancer and neurodegenerative disorders [60], few studies have specifically examined the associations between adherence to the mediterranean diet and sarcopenia. However, in a cross-sectional study on women, 45 years or older, the mediterranean diet was associated with lower odds of sarcopenia when compared with a western diet (high in processed foods, sugar, solid fat, and fast food) [61]. Sarcopenia is a core component of physical frailty and there have been studies showing the beneficial effects of the mediterranean diet on frailty. For example, Bollwein et al. [62] found that in adults aged >75 years greater compliance with the mediterranean diet was associated with a significantly reduced prevalence of frailty. Similar findings were observed in community-dwelling adults aged >65 years after 6-year follow-up where compliance to the mediterranean diet was associated with a lower risk of developing frailty [63]. A meta-analysis of four observational studies found that greater adherence to the mediterranean diet was significantly associated with a reduced risk of frailty (OR = 0.44, 95% CI = 0.31-0.64, $P < 0.001$, for a mediterranean diet score of 6-9 [64].

3. Conclusions

Sarcopenia is a growing public health problem in a rapidly ageing population. However, a lifecourse approach focusing on interventions in adolescence and adulthood to maximise peak gain in muscle function, and in later life to slow the decline in muscle function is gathering importance. This can be achieved through multimodal approaches combining resistance exercise and nutritional supplementation with a focus on enhancing the amount, frequency and variety of dietary protein, vitamin D and antioxidative nutrients. Although this approach appears to represent a cornerstone of therapy for sarcopenia more well conducted research studies urgently required [65].

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Author Contributions

All authors made substantial contributions to the conception of this review and have approved the submitted version.

Competing Interests

Harnish P Patel has received lecture fees from Abbott, Pfizer, and HC-UK conferences outside of the submitted work. Faidra Laskou declares no conflicts of interest. Elaine Dennison has received speaker and consultancy fees from Viatris, UCB and Pfizer, not related to the material reviewed here.

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